MULTIPLE SCLEROSIS AND NEUROCHEMICAL DISTURBANCES

Vladimir V. Markelov[1], Maxim V. Trushin[2]

ABSTRACT

The data presented in this manuscript suggest a pivotal role of the central nervous system (CNS) in the regulation of immune status. We describe here that some neurochemical disturbances may provoke development of various diseases including multiple sclerosis. Some theoretic and practical backgrounds, how to improve the multiple sclerosis sufferers and patients with other autoimmune disorders, are also given.

KEY WORDS: Multiple sclerosis, Neurotransmitters, Tryptophan, Immunomodulation.

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INTRODUCTION

A bulk of studies devoted to multiple sclerosis (MS) is concentrated on therapy of the disease while studies on the MS pathogenesis are not so common. Risk factors include presence of various microorganisms (human herpesvirus 1 and 6 (HHV-1 and 6) and Epstein-Barr virus (EBV), papovavirus, Semliki Forest virus, Visna virus, varicella zoster virus, *Chlamydia pneumoniae*, some mycoplasmas). These are associated with development of MS and its animal analougs.[1-12] In this situation, it is clear that Koch's paradigm "one organism, one disease" cannot be applied to such inscrutable disease like MS. It is very speculative to associate any disease with any microorganism until the whole population is not tested on the carriage of the same microbe. Epidemiologists understand that it is a very difficult task. Unfortunately, the similar situation is observed in the MS genetics: at least 32 alleles of the major histocompatibility complex (MHC) are associated with the MS development.[13, 14]

In our view, the most logic are concepts that connect the MS pathogenesis with the dialogue disturbance between the nervous and immune systems, particularly due to imbalance of neurotransmitters. In this manuscript we have attempted to point out some issues associated with this problem.

THE ROLE OF THE NEUROTRANSMITTER IMBALANCE IN MS AND SOME OTHER DISEASES

It is known that imbalance of neurotransmitters is the obligate condition in the MS patients as well as in people with other somatic and psychiatric disorders. Moreover, some research groups showed evidently that reversibility of normal signalization within the CNS might result in normalization of functioning of various organs and systems.[15]

Currently, neurological manifestations of MS are generally associated with the axon demyeliniation, which is considered as an examination criterion.[16] However, clinical data suggest that a strong correlation between brain lesions and clinical presentation is absent. For example, as far back as late sixties researchers

1. Dr. Vladimir V. Markelov
Kazan Municipal Rehabilitation Medical Health Center "Sanatorium Krutushka",
P.O. Box: 420130,
Kazan, - Russia.
2. Dr. Maxim V. Trushin
Kazan Institute of Biochemistry and Biophysics,
P.O. Box: 30,
Kazan - 420111, Russia.

Correspondence:

Dr. Maxim V. Trushin
E-Mail: mtrushin@mail.ru

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showed that the vision recovery after the optic neuritis episode cannot be explained by remyelination.[17] Moreover, it is known that sometime people with intensive demyeliniation events may have no neurological deficit.[18] Also, brain lesions and the spinal cord lesions may be observed accidentally in people long before development of the first clinical signs of MS.[19-22] The accumulated data suggest that the MS challenges cannot be considered as the direct manifestation of demyeliniation and that other possible factors, particularly imbalance of neurotransmitters, should be taken into account.

About thirty years ago, the level of 5-hydroxyindoleacetic acid (5-HIAA) was shown to be decreased in the cerebral spinal fluid of patients with MS.[23,24] Additionally, the level of the above-mentioned metabolite of serotonin was more decreased in the most severely disabled MS patients.[25] So, the available data confirm a correlation between the level of cerebral serotonin and the disease course.

Since the beginning of sixties of the last century, intensive investigations of neurotransmitters and their metabolites were carried out in the Institute of Experimental Medicine (Caracas, Venezuela). Over 30000 healthy and diseased individuals were analyzed and some general conclusions were made. In particular, the investigators showed that patients with Th-1 immune profile (increased cellular immunity) display neurochemical features similar to those observed in major depression.[15] Namely, in patients with MS, Grave's ophthalmopathy, Crohn's disease, rheumatic arthritis, psoriasis and many others, a similar neurochemical disturbances are observed: increased norepinephrine to epinephrine ratio plus decreased level of tryptophan in the blood plasma. Alternatively, in Th-2 diseases (increased humoral immunity) – myasthenia, thrombocytopenic purpura, hemolytic anemia and others – the opposite neurochemical defects are detected (profile of maladaptation to stress).[15] Numerous studies by these authors have demonstrated that management of the observed neurotransmitter imbalance may result in improvement of patients. Moreover, one therapeutic modality may work efficiently in patients with different disorders (Th-1 or Th-2 diseases).[26-30]

It should be noted here that many studies have confirmed an association between activity of immune and nervous systems.[31,32] Immunological changes observed in the MS patients are similar to those detected in the major depressed patients.[33] It is also known that depletion of the serotonin neurotransmission may be mediated by activation of indoleamine-2,3-dioxygenase (IDO) by inflammatory cytokines.[33] Some reseachers showed that the tryptophan derivates (3-hydroxy-kynurenine (3OH-KYN) and quinolinic acid (QUIN) arisen in the kynurenine cycle have neurotoxic effect.[34,35] Increased level of the above-mentioned metabolites is detected in neurodegenerative diseases and major depression.[34-36] In turn, 3OH-KYN is able to induce the reactive oxygen species formation whose cytopathogenic effect is some well documented.[37] Thus, the accumulated scientific data suggest neurochemical disturbances including psychosomatic disorder are important in any neurological disease as reported by investigators.[15] Therefore, prescription of some appropriate neurotrophic drugs which are able to restore neurotransmitter balance may be useful in many autoimmune diseases including MS.

SOME STEPS IN THE MS NEUROIMMUNOMODULATION

According to some authors[15] enhancement of the central serotonin neurotransmission is an important step. The simplest way to increase serotonin neurotransmission is administration of the serotonin precursors like L-tryptophan and 5- hydroxytryptophan (5-HTP); the second might be synthesized in the human organism from the former. However, 5-HTP (a commercial product produced from the seeds of the African plant *Griffonia simplicifolia*) became the most popular and is used in clinical practice since the last seventies.[38] Efficiacy of 5-HTP was confirmed in fibromyaligia,

insomnia, chronic headaches and some other pathology.[39] This substance crosses the blood-brain barrier without difficulties, and increases significantly the serotonin synthesis in the CNS.[40] Many factors (vitamines and minerals) may enhance this process. We have to note here that glucocorticoids frequently used for treatment of MS are able to induce IDO (an enzyme participating in the tryptophan catabolism) a fact that is known since 1980s.[41]

In 1987, the selective serotonin reuptake inhibitors (SSRI) were introduced into clinical practice. Initially, this type of antidepressants were used exclusively in psychiatric practice. However, during the last decade, some immunological activities of these drugs were described. At present, it is known that SSRI can cause significant decrease in synthesis of inflammatory cytokines and increase in the production of anti-inflammatory ones [42-45] as well as mediate reduction of the interferon-á to interleukin 10 (INF- á/IL-10) ratio whose importance for T-cell activation was shown previously.[46]

The presence of the increased levels of inflammatory cytokines in the MS patients was confirmed by many studies.[47-49] Therefore, we consider that application of SSRI and other serotonin promoting substances with the immune downregulation properties is reasonable. Moreover, there were some positive results: administration of L-tryptophan to the MS patients resulted in improvement of autonomic, motor and sensory functions.[50] Expediency of the SSRI administration in the MS patients is currently under discussion.[51] This type of antidepressant was shown to have anti-inflammatory and anti- asthenia [52,53] besides having analgesic action [54, 55] which is very important for the MS sufferers.

CONCLUSIONS

The presented material shows an important role of interaction between the CNS and immune system.[15,56,57] A vast experience obtained in the Institute of Experimental Medicine (Caracas, Venezuela) confirms the possibility to manage some autoimmune diseases without development of relapse during a long time.[15,26-30] In addition, application of some physiotherapeutic procedures with the prior proserotonergic therapy contributes to general improvement and long-term remission in the MS patients.[58-60] We hope that neurologists engaged in the MS study will find this information useful.

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